BAP1: role in carcinogenesis and clinical implications

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Abstract: BRCA-1 associated protein 1 (*BAP1*) is a tumor suppressor gene that has been implicated in the pathogenesis of several malignancies and is gaining more recognition as a crucial gene that could be amenable to therapeutic manipulation. There is a growing interest in prevention and establishing cancer screening guidelines in patients with germline *BAP1* mutations to aid with early detection and treatment of associated malignancies. We aim to give a concise review of *BAP1* and its role in carcinogenesis, the *BAP1* cancer predisposition syndrome and discuss clinical implications including suggested screening guidelines, and potential targeted therapeutic options.

Keywords: BRCA-1 associated protein 1 (*BAP1*); germline; cancer; mesothelioma; genetics

Introduction

BRCA-1 associated protein 1 (*BAP1*) is a tumor suppressor gene of which germline mutations lead to predisposition of several malignancies. The *BAP1* gene, located on chromosome 3p21.1, was discovered by Jensen and colleagues in 1998 (1). *BAP1* encodes for a multi-domain protein, BAP1 protein, which contains a N-terminal ubiquitin carboxyl hydrolase (UCH) domain, a host cell factor 1 (HCF-1) binding motif (HBM) domain, and a variety of other binding regions for different protein interactions (1,2). BAP1 functions as a tumor suppressor deubiquitinating enzyme, modulating gene transcription, cellular differentiation, and DNA damage repair, apoptosis and cell metabolism (3-5). Through genomic analyses of family members with both uveal melanoma (UM) and malignant mesothelioma (MM), two rare and unrelated malignancies, a cancer predisposition syndrome implicating germline mutations in *BAP1* was discovered and was named as BAP1 tumor predisposition syndrome (BAP1-TPDS) (3). Germline *BAP1* inactivation is an autosomal dominant disease with high penetrance and increases susceptibility to MM, cutaneous melanoma, UM, clear cell renal cell carcinoma (ccRCC), cholangiocarcinoma, basal cell carcinoma, and likely other malignancies (3,6,7). There has been increased interest in the mechanisms by which *BAP1* mutations lead to carcinogenesis. Recently, screening guidelines have been proposed for patients harboring germline *BAP1* mutations to aid with early cancer detection. We aim to give a concise review of the carcinogenesis caused by *BAP1* mutations, and discuss clinical implications including suggested screening guidelines for patients with germline *BAP1* mutations, and potential targeted therapeutic options in patients with mutated *BAP1*.

BAP1 and carcinogenesis

BAP1 interacts with proteins that regulate gene expression, such as HCF-1, O-linked N-acetylglucosamine transferase (OGT), and the polycomb group proteins ASXL1 and ASXL2 (8). BAP1 is required for embryogenesis, evident by *BAP1*$^{-/-}$ murine embryos showing developmental

retardation at embryonic day 8.5 and subsequent embryonal death (8). Loss of *BAP1* in hematopoietic cells induces a phenotype consistent with myelodysplasia and ineffective erythropoiesis (8).

Following DNA damage by ultraviolet (UV) light, there is an increase in BAP1 phosphorylation (9). BAP1 deubiquitylates Ub-H2AK119 at sites of DNA damage, and the loss of BAP1 has been shown to impair homologous recombination (HR) repair (10). The recruitment of BAP1 to sites of UV-induced DNA damage was found to be dependent on poly (ADP ribose) polymerase 1 and 2 (PARP1 and PARP2) (10). BAP1 also controls the accumulation of other DNA-repair proteins (BRCA1, RAD51, and RPA) at sites of DNA damage (10). Given these experimental findings, it is not surprising that a *BAP1*-mutated RCC cell line treated with a PARP inhibitor, olaparib, showed decreased cell viability (11). Moreover, malignant pleural mesothelioma (MPM) cell lines expressing a BAP1 splice variant with defective deubiquitinating activity treated with olaparib also showed markedly decreased cell viability (12). Clinical trials are underway to investigate the role of PARP inhibitors in patients with DNA-repair protein defects, including BAP1. Currently there is one trial of niraparib (PARP inhibitor) (Clinicaltrials.gov ID NCT03207347) and three trials investigating olaparib (another PARP inhibitor) in BAP1 and other DNA damage response (DDR) deficient neoplasms (Clinicaltrials.gov ID NCT03786796, NCT03531840, NCT03375307).

Mutations in *BAP1* most often affect its catalytic activity (10). Components of polycomb repressive complex 2 (PRC2) are overexpressed in various malignancies such as melanoma, lymphoma, breast and prostate cancer (13). Loss of BAP1 results in accumulation of methylated histone H3 lysine 27 (H3K27) and suppression of PRC2 targets (14). Enhancer of zeste homolog 2 (EZH2) is a protein component of the PRC2 involved in chromatin modification and is one of the two essential catalytic enzymes for the methylation H3K27 in mammalian cells (14). Analysis of The Cancer Genome Atlas (TCGA) data revealed EZH2 mRNA expression was increased in mesothelioma tumor samples compared to matched controls (15). Silencing EZH2 induced apoptosis in *BAP1*-mutant mesothelioma cell lines (15). EZH2 inhibition also reduced mesothelioma tumor size in *BAP1*-mutant mice (15). In contrast, Schoumacher and colleagues showed EZH2 was not overexpressed in UM cases, and subsequently UM cases

with BAP1 loss were insensitive to the EZH2 inhibitor, EPZ-6438 (16). These findings highlight the tissue-dependent expression of epigenetic regulators and differing roles in carcinogenesis. Tazemetostat (an EZH2 inhibitor) has been tested in mesothelioma patients with BAP1 loss-of-function and shoed some promising activity. The disease control of tazemetostat was 51% at 12 weeks and 25% of patients-maintained disease control at 24 weeks (17).

Recent studies have described that cells from *BAP1* mutant carriers constitutionally derive a large part of their energy through aerobic glycolysis (18). The Warburg effect is a phenomenon in which cancer cells adapt to an anaerobic environment to promote cell growth (18). Cancer cells, thus, acquire the same amount of energy from fermentation as from the tricarboxylic acid (TCA) cycle (18). Normal fibroblast cell cultures in individuals with heterozygous loss of *BAP1* exhibited increased glycolysis and decreased aerobic mitochondrial respiration (5). There were significant differences in glycolysis and the signature of TCA cycle metabolites between *BAP1* wild-type (WT) and *BAP1* mutant fibroblast cell cultures (5). The Warburg effect promotes carcinogenesis by altering cell metabolism in both tumor cells and surrounding stromal cells (19). Consistent with this observation, germline mutations in *BAP1* alter cellular metabolism and tumor microenvironment promoting malignant transformation of cells (18). In another report, BAP1 was found to modulate endoplasmic reticulum (ER)-mitochondria calcium release (4). BAP1 was found to localize to the ER where it regulates Ca^{2+} release by binding to the type 3 inositol 1,4,5 triphosphate receptor (IP3R3), promoting apoptosis (4). DNA damaged cells appear to be particularly susceptible to cancer transformation due to decreased apoptosis in individuals with deficient BAP1 (4).

BAP1 cancer syndrome

The majority (>95%) of BAP1 inactivated tumors are due to sporadic mutations in the gene. Since the report of germline mutations predisposing to mesothelioma and UM in two large and distant families (W from Wisconsin and L from Louisiana) (20), there has been a growing interest in reporting detailed family pedigrees with known *BAP1* mutations and associated cancer susceptibilities. The average age of onset of various malignancies, including mesothelioma, in 8 different families with known germline *BAP1* mutations ranged from 40–60 years (21). Similar results were found in a study of 79 patients selected on the

basis of specific criteria related to family history of cancer and diagnosis at younger age. Within this cohort, 13 out of 33 patients with diagnosis of mesothelioma before the age of 50 years carried germline *BAP1* mutations and 12 of them had an extensive family history of malignancies associated with the BAP1 cancer syndrome. Interestingly, these patients had a significantly improved survival over sporadic mesothelioma cases (22). Most cancers associated with inactivation of *BAP1* occur at ages earlier than those seen in sporadic cases, and some as early as teenage years (23). The majority of patients with germline *BAP1* mutations have been diagnosed with at least one malignancy (23). The spectrum of tumors observed in *BAP1*-mutant murine models was similar irrespective of the type or location of the *BAP1* mutation (24). Below we discuss the data surrounding the most commonly diagnosed malignancies in individuals with germline *BAP1* mutations which include MM, cutaneous melanoma, UM, and ccRCC.

Malignant mesothelioma

MM originates from mesothelial cells of the pleura (80–90%), peritoneum (10–15%) or rarely the pericardium (<5%) (25,26). High rates of non-synonymous mutations in *BAP1* were found in MPM tumor samples (27). The same study showed 42% of MPM tumors harbored either *BAP1* loss, mutation or both. *BAP1* deleterious germline mutations have been reported with varying frequency in patients with MM ranging from 3–31% (22,28,29). The median age at diagnosis of MM was 54.5 years in patients with germline *BAP1* mutations, which is younger than patients with WT *BAP1*. The anatomical distribution of MM in individuals with germline *BAP1* mutations is different than sporadic cases. Approximately one-half of mesothelioma in *BAP1* mutated individuals originates in the pleura and the other half manifest with peritoneal disease (30). Sporadic mesotheliomas, on the other hand, are more frequently diagnosed with pleural rather than peritoneal primary (30).

BAP1 mutant mice have a shortened survival compared to WT mice after exposure to asbestos (31,32). Survival difference could be attributed to earlier development of mesothelioma and death in *BAP1* mutant mice after asbestos exposure. Investigators showed that $BAP1^{+/-}$ mice compared with *BAP1* WT mice exposed to asbestos had increased susceptibility of MM (73% *vs.* 32%, respectively) leading to decreased survival (31). Mice carrying germline $BAP1^{+/-}$ developed mesothelioma after exposure to doses of

asbestos about ten-times lower doses than those inducing mesothelioma in WT mice (32). Observational studies in humans have demonstrated the opposite in terms of survival. Individuals with *BAP1* mutations and MM have a significantly increased median overall survival (OS) (60 months) compared to those WT *BAP1* individuals (17 months) (28). Baumann *et al.* showed that median OS was 5 years in 23 patients with MM and germline *BAP1* mutations (30). Screening for *BAP1* germline mutations should be considered in patients with MM who have a family history of MM, UM, cutaneous melanoma, RCC, cholangiocarcinoma, basal cell carcinoma, and/or a high family incidence of multiple cancers (33). Screening can also be considered in patients with MM who are found to have melanocytic *BAP1*-mutated atypical intradermal tumors (MBAITs) (33). There are currently no established guidelines for cancer screening in *BAP1* mutation carriers other consensus and multidisciplinary expert panel recommendations (34,35). These recommendations are already being used in clinical practice to screen patients and family of patients with *BAP1* germline mutations (36).

Suggested screening tests for MM in germline BAP1 mutated individuals (34)

Begin annual abdominal and respiratory physical examinations starting at 30 years of age. Imaging surveillance using ultrasound (US) or magnetic resonance imaging (MRI) of the chest and/or abdomen can be considered for asymptomatic patients between ages 30–55 every 2 years. In those individuals >55 years of age, consider either computed tomography (CT) chest/abdomen or MRI chest/abdomen with intravenous (IV) contrast every 2 years. A diagnostic fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is not recommended as first-line imaging modality due a higher ionizing radiation dose. If cost is not prohibitive, a renal and chest US can be considered in the years between CT or MRI.

Uveal melanoma

Gene expression profiling has classified UMs into two main types: low (class 1) and high (class 2) metastatic potential (37). Class 2 tumors contain dedifferentiated cells and have a primitive neuroectodermal cells gene signature (38). There is a high prevalence of somatic *BAP1* mutations in class 2 UMs (39). Eighty-four percent of UMs sampled by Harbour and colleagues showed *BAP1* mutations (39).

Germline mutations in *BAP1* were discovered in 3/53 (5.7%) of cases of UM (40). Age of onset was much younger in individuals with germline *BAP1* mutations compared to *BAP1* WT individuals (39).

Suggested screening tests for UM in germline BAP1 mutated individuals (34)

An annual ophthalmic exam by a UM specialist should begin at age 16 and biannual exams after age 30 years is recommended, consisting of direct and indirect ophthalmoscopy, fundus photography, and ocular US. Exams starting at a younger age should be considered if there is a family history of UM.

Melanocytic tumors and cutaneous melanoma

A new melanocytic neoplasm was described by Wiesner and colleagues with an autosomal dominant inheritance pattern in two unrelated families (34). All affected family members developed skin-colored, dome-shaped, well-circumscribed papules that varied in size and number (41). These tumors appeared during the second decade of life. Through genomic sequencing of the melanocytic tumor specimens, a frameshift mutation in *BAP1* was identified (41). The term melanocytic *BAP1*-MBAIT has been previously coined to describe these skin lesions (3,33). The majority of familial epithelioid Spitz tumors or MBAITs have biallelic loss of *BAP1* via *BAP1* germline mutation, 3p21.1 chromosomal deletion, or uniparental disomy (7).

Cutaneous melanoma develops in approximately one-third of individuals with germline *BAP1* loss (41). The role of BAP1 in melanocytic neoplasia depends on the presence of associated oncogenes (41). The median age at diagnosis of cutaneous melanoma was 41 years in a cohort of 38 patients with germline *BAP1* mutations (21). The estimated penetrance of MBAITs and cutaneous melanoma in patients with germline *BAP1* mutations was reported to be 17% and 18%, respectively, although may be as high as 75% (21).

Suggested screening tests for cutaneous melanoma in germline BAP1 mutated individuals (34)

Perform biannual dermatologic examinations by a melanoma specialist, including full-skin examination with systematic review of total body photography (TBP) starting at 18 years. Sequential digital dermatoscopic monitoring or excision of any mildly irregular skin lesion can be considered.

Renal cell carcinoma

RCC due to inheritable genetic mutations may account for 2–4% of cases (42). Mutations in genes involved in the ubiquitin-mediated proteolysis pathway (UMPP) activating the hypoxia regulatory network were found in 50% of ccRCC cases (43). Somatic inactivation of *BAP1* has been demonstrated in 8-14% of ccRCCs (11,43). BAP1 functions as a two-hit tumor suppressor in ccRCC and no second hit point mutations or deletions were found in tumors with *BAP1* mutations (11). This is in opposition to MM and cutaneous melanoma studies which show loss of both *BAP1* alleles (39,44). An association between high tumor grade and mTORC1 activation has been linked to *BAP1* loss (11). One study of families with germline mutations in *BAP1* showed 6 of 11 families were affected by ccRCC (42). Nine total cases of ccRCC were detected in these families, suggesting mutated *BAP1* plays a role in ccRCC oncogenesis and may increase risk of ccRCC by 8-fold (42).

Suggested screening tests for RCC in germline BAP1 mutated individuals (34)

Recommend annual abdominal physical examinations starting at age 30. Imaging surveillance using US or MRI can be considered for asymptomatic patients at age 30–55 every 2 years. After 55 years of age, perform CT chest/abdomen or MRI chest/abdomen every 2 years, both with IV contrast.

Other malignancies

Among patients with meningiomas with rhabdoid features, 10% were found to have loss of BAP1 by immunohistochemistry (45). Two of these patients had detectable germline mutations in *BAP1*, one with a splice site mutation and the other with a nonsense mutation. Other histologic features in this cohort of patients included sheets of dedifferentiated cells and epithelioid-type cells with a papillary growth pattern (45). Meningiomas with germline loss of *BAP1* followed a more aggressive clinical course compared to WT tumors (45). A majority of meningiomas with *BAP1* inactivation were classified as WHO grade 2–3.

Jensen and colleagues showed two non-small cell lung cancer (NSCLC) cell lines had undetectable levels of BAP1 expression, suggesting that BAP1 may be a target

for inactivation or down-regulation during NSCLC pathogenesis (1). In a family with known truncating germline mutation of *BAP1*, lung adenocarcinoma was diagnosed in the proband (40). Other tumors that were reported to be associated with germline *BAP1* mutations include breast cancer, ovarian cancer non-melanoma skin cancer, cholangiocarcinoma, leiomyosarcoma, neuroendocrine cancer, pancreatic cancer, and paragangliomas (3).

Treatment implications

Clinical research continues to establish treatment implications for patients with *BAP1* loss, whether somatic or germline. Histone deacetylase (HDAC) inhibitors reversed the H2A hyperubiquitination caused by *BAP1* loss, and they shifted the gene expression profile of class 2 cells toward a class 1 profile in a UVM cell line (44). HDAC inhibitors, thus, may slow the rate of metastatic spread of UVM cells and change the disease to a less aggressive phenotype (44). A phase 3 study comparing vorinostat (a HDAC inhibitor) with placebo in relapsed or refractory MPM concluded vorinostat did not improve OS compared to placebo and led to a statistically significant but not clinically relevant improvement in PFS (46). Molecular analysis to detect *BAP1* mutations in patients treated on this study has not been reported (46). *BAP1* loss leads to increased expression of EZH2 (15). EZH2 inhibitors are a potential therapeutic strategy for BAP1-deficient tumors as mentioned previously.

PARP inhibition is another potential targeted therapy option in patients with somatic or germline *BAP1* mutations. Clinical trials are underway to investigate the role of PARP inhibitors in patients with DNA-repair protein defects, including BAP1. Currently there is one trial of niraparib (PARP inhibitor) (Clinicaltrials.gov ID NCT03207347) and three trials investigating olaparib (another PARP inhibitor) in BAP1 and other DDR deficient neoplasms (Clinicaltrials. gov ID NCT03786796, NCT03531840, NCT03375307).

A recent study published by Hassan *et al.* suggested that patients with pleural mesothelioma with loss-of-function mutations in *BAP1* and other DNA repair genes appeared to benefit from platinum chemotherapy compared with patients without inherited mutations (47).

Conclusions

Physicians and other healthcare professionals caring for patients with mesothelioma should be educated about BAP1-TPDS and potential alarming symptoms in *BAP1*

germline mutation carriers that require evaluation by a specialty or multidisciplinary clinic. Educating *BAP1* germline mutation carriers and their family members is equally important. Particular attention should be given to symptoms including anorexia, weight loss, abdominal pain, respiratory symptoms, visual symptoms, and new or changing skin lesions. Patients should be educated on general cancer prevention strategies like avoiding asbestos and tobacco exposure as well as applying sunscreen before going outdoors. There are no established guidelines for screening patients for germline *BAP1* mutations. Family predisposition to rare cancers such as UM or MM should raise the concern for an underlying germline *BAP1* and should be taken into consideration when making individualized screening recommendations.

Identifying individuals with *BAP1* germline mutation may trigger further testing in other family member to identify other at-risk family members. Germline testing should be considered in the context of genetic counseling. Children of individuals with germline *BAP1* mutations should consider testing at age 18 to facilitate appropriate cancer screening. Testing in younger individuals may require more complex decision making that should take into account the ethical framework of autonomy, justice, beneficence and maleficence. Finally, there are currently no specific therapies approved by the FDA for treatment of *BAP1* mutant carriers with cancer, and this is an ongoing area of active research.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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